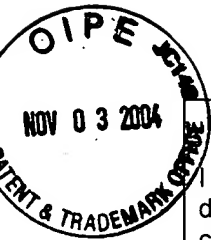


COPY



CASE DB 17/Div1

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

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November 1, 2004
Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

WITTEKIND et al

PATENT NO: 6,800,456 B2

ISSUED: Oct. 5, 2004

FOR: MODIFIED FORMS OF HEPATITIS C NS3
PROTEASE FOR FACILITATING INHIBITOR SCREENING AND STRUCTURAL
STUDIES OF PROTEASE: INHIBITOR COMPLEXES

Certificate
NOV 05 2004
of Correction

Assistant Commissioner for Patents
Washington, D.C. 20231

Attention: Decision and Certificate of Correction
Branch of Patent Issue Division

Request for Certificate of Correction of Patent for PTO Mistake (37 C.F.R. §1.322(a))

Sir:

Attached in duplicate, is Form PTO -1050 for use in correcting errors in U.S. Patent No. 6,800,456 B2 not due to Applicants' mistake.

Please forward the Certificate to the address associated with Customer No. 23914.

If any fee not accounted for is due in connection herewith, please charge such fee to Deposit Account No. 19-3880 of the undersigned.

Respectfully submitted,

Audrey F. Sher
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Date: November 1, 2004

NOV 10 2004



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DB17-US-DIV 1

Sher

(12) **United States Patent**
Wittekind et al.

(10) **Patent No.:** **US 6,800,456 B2**
(45) Date of Patent: **Oct. 5, 2004**

(54) **MODIFIED FORMS OF HEPATITIS C NS3
 PROTEASE FOR FACILITATING INHIBITOR
 SCREENING AND STRUCTURAL STUDIES
 OF PROTEASE:INHIBITOR COMPLEXES**

(75) **Inventors:** **Michael Wittekind**, Doylestown, PA
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(73) **Assignee:** **Bristol-Myers Squibb Company**,
 Princeton, NJ (US)

(*) **Notice:** Subject to any disclaimer, the term of this
 patent is extended or adjusted under 35
 U.S.C. 154(b) by 327 days.

(21) **Appl. No.:** **09/965,594**

(22) **Filed:** **Sep. 27, 2001**

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Related U.S. Application Data

(62) Division of application No. 09/478,479, filed on Jan. 6,
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(60) Provisional application No. 60/115,271, filed on Jan. 8,
 1999.

(51) **Int. Cl.⁷** **C12P 21/06; C07H 21/04**

(52) **U.S. Cl.** **435/69.1; 435/320.1; 435/325;
 536/23.2; 536/23.4**

(58) **Field of Search** **435/69.1, 320.1,
 435/325; 536/23.2, 23.4**

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,371,017 A	12/1994	Houghton et al.
5,585,258 A	12/1996	Houghton et al.
5,597,691 A	1/1997	Houghton et al.
5,712,145 A	1/1998	Houghton et al.
5,739,002 A	4/1998	DeFrancesco et al.
5,843,752 A	12/1998	Dasmahapatra et al.

FOREIGN PATENT DOCUMENTS

WO	WO 91/15575	10/1991
WO	WO 95/22985	8/1995
WO	WO 96/36702	11/1996
WO	WO 97/08304	3/1997
WO	WO 98/11134	3/1998
WO	WO 98/12308	3/1998

OTHER PUBLICATIONS

Love et al., Cell 87:331-342 (1996).
 Kim et al., Cell 87:343-355 (1996).
 Ingallinella et al., Biochemistry 37:8906-8914 (1998).
 Yan et al., Protein Science 7:837-847 (1998).
 Taremi et al., Protein Science 7:2143-2149 (1998).
 Keutmann et al., Molecular Endocrinology 6:904-912
 (1992).
 Bianchi et al., J. Mol. Biol. 236:649-659 (1994).

DeFrancesco et al., 35:13282-13287 (1996).

Choo et al., Science 244:359-362 (1989).

Kuo et al., Science 244:362-364 (1989).

Choo et al., Proc. Of Natl. Acad. of Sciences 88:2451-2455
 (1991).

Grakoui et al., Journal of Virology 67:2832-2843 (1993).

Bartenschlager et al., Journal of Virology 67:3835-3844.

Grakoui et al., Journal of Virology 67:1385-1395 (1993).

Hijikata et al., Proc. Of Natl. Acad. of Sciences
 90:10773-10777 (1993).

Tomei et al., Journal of Virology 67:4017-4026 (1993).

Bartenschlager et al., Journal of Virology 68:5045-5055
 (1994).

Eckart et al., Biochem. And Biophys. Res. Commun.
 192:399-406 (1993).

Lin et al., Journal of Virology 68:8147-8157 (1994).

Manabe et al., Virology 198:636-644 (1994).

Chambers et al., Proc. Of the Natl. Acad. of Sciences
 87:8898-8902 (1990).

Xu et al., Journal of Virology 71:5312-5322 (1997).

Overton et al., Journal of General Virology 71:5312-5322
 (1994).

Bartenschlager et al., Journal of Virology 71:5312-5322
 (1995).

Bouffard et al., Virology 209:52-59 (1995).

Tanji et al., Journal of Virology 69:1575-1581 (1995).

Lin et al., Proc. Of Natl. Acad. Sciences 92:7622-7626
 (1995).

Satoh et al., Journal of Virology 69:4255-4260 (1995).

Tanji et al., Gene 145:215-219 (1994).

Failla et al., Journal of Virology 69:1769-1777 (1995).

Shojo et al., Hepatology 22:1648-1655 (1995).

Lin et al., Journal of Virology 69:4373-4380 (1995).

Tomei et al., Journal of General Virology 77:1065-1077
 (1995).

Shimizu et al., Journal of Virology 70:127-132 (1996).

Lin et al., Proc. Of the Natl. Acad. Sciences 92:7622-7626
 (1995).

Suzuki et al., Journal of General Virology 76:3021-3029
 (1995).

Hong et al., Journal of Virology 70:4261-4268 (1996).

Steinkuhler et al., Journal of Virology 70:6694-6700 (1996).

Inoue et al., Biochem. and Biophys. Res. Commun.
 245:478-482 (1998).

(List continued on next page.)

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 (74) **Attorney, Agent, or Firm**—Andrew F. Sher

(57) **ABSTRACT**

The present invention relates to modified Hepatitis C NS3
 proteases and modified Hepatitis C NS4a-NS3 fusion pro-
 teases. These proteins are highly soluble and are useful for
 NMR spectroscopy, X-ray crystallography, and inhibitor
 screening. DNA constructs are also provided.

15 Claims, 18 Drawing Sheets

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO : 6,800,456 B2
DATED: : October 5, 2004
INVENTOR(S) : WITTEKIND ET AL.

It is certified that there is an error in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On Cover Sheet

Section (75) Inventors: Michael Wittekind, Doylestown, PA (US); Steven Weinheimer, Northford, CT (US); Yagun Zhang, Holland, PA (US); Valentina Goldfarb, Franklin Park, NJ (US)

Section (74) *Attorney, Agent, or Firm* – Andrew F. Sher

should read

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